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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CARTER, KENDRA D	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,839	FUKUNAGA ET AL.	
	Examiner	Art Unit	
	KENDRA D. CARTER	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,12,13,17-20 and 22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,12,13,17-20 and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 10, 2007 has been entered.

The Examiner acknowledges the applicant's remarks and arguments of October 10, 2007, November 5, 2007 and November 13, 2007 made to the office action filed May 10, 2007. Claims 9, 12, 13, 17-20 and 22-27 are pending. Claims 9 and 25 are amended and claims 26 and 27 are new. Claims 1-8, 10, 11, 14-16 and 21 are cancelled

In light of the amendments, the 35 U.S.C. 112, first paragraph rejection of claims 9, 12-13, 17-20 and 22-25 is withdrawn.

For the reasons in the previous office action and below, the Applicant's arguments of the following rejections were found not persuasive, thus the rejections are

upheld: 1) 35 U.S.C. 112, first paragraph rejection of claim 25; and the 35 U.S.C. 103 (a) rejection of claims 9 and 12-25as being unpatentable over Asano et al. in view of Finkenaur.

Due to the addition of new claims and amendment to the claims, the modified and 35 U.S.C. 112, first paragraph and 103(a) rejections are made below. The Applicant's remarks and declaration are addressed below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification as originally filed does not provide support for the viscous preparation that "retains bFGF activity at 25°C at a remaining ratio of at least 98.9% level for at least 42 hours," as recited in the newly added claim. The specification discloses that for the particular preparations Ia and Ib

having a specific content of thickener and bFGF, that a remaining ratio remaining after 42 hours was 99.1 and 98.9 (see Table I, in particular), not at least 98.9. The specification does not teach that a remaining ratio was higher than 98.9% for all viscous preparations in general, having and content of the bFGF and hydroxypropyl cellulose. Accordingly, claim 25 recites impermissible new matter, and is rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9 and 12-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,046,164 to Asano et al, issued April 4, 2000, in view of EP 0 267 015 to Amy L. Finkenaur, published May 11, 1988.

Asano et al. teaches a method for treating diseases of periodontal tissue by administering a basic fibroblast growth factor (see abstract, in particular.) Asano et al. teaches that the bFGF can be prepared in various formulations, including liquids by combining bFGF with a pharmacologically acceptable additive, such as a solvent,

stabilizer, etc. (see column 4, lines 4-15, in particular.)

Asano et al. does not specifically teach providing hydroxypropyl cellulose in the bFGF composition, as recited for example in claim 9.

Finkenaur teaches that a stabilizing effective amount of a water-soluble polysaccharide can be provided in medicinal compositions containing a polypeptide growth factor with mitogenic activity to stabilize the polypeptide growth factor against loss of biological activity in the presence of moisture (see abstract, in particular.) Finkenaur teaches that basic fibroblast growth factor is an example of such as polypeptide growth factor that can be stabilized with the polysaccharide (see page 3, lines 25-30, in particular.) Finkenaur further teaches that the polysaccharides act to increase the viscosity of the composition (see page 4, lines 55-65, in particular), and thus are thickeners. Finkenaur teaches that the stabilizing polysaccharide for stabilizing the polypeptide growth factor can be selected from among polysaccharides including methyl cellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose, and hydroxypropyl cellulose (a hydroxypropyl ether derivative of cellulose), as in claim 9 (see page 3, lines 35-50, in particular.)

Regarding the recitation that hydroxypropyl cellulose contains 53.4-77.7% of hydroxypropyl group, as in claim 9, Finkenaur teaches that the solubility of the cellulose derivatives is determined by degree of substitution of the ether groups, and teaches that

a suitable degree of ether substitution may be at least 0.35 ether groups per anhydroglucose unit (see page 3, lines 44-50, in particular.) Furthermore, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount of ether substitution of the celluloses, according to the guidance provided by Finkenaur, to provide a composition having desired properties, such as desired solubility. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955.)

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to incorporate the hydroxypropyl cellulose stabilizer/thickener of Finkenaur into the bFGF composition taught by Asano et al. and administer for the treatment of periodontal disease, because Asano et al. teaches that a composition comprising bFGF and a stabilizer can be administered for the treatment of periodontal disease, and Finkenaur teaches that polysaccharides such as hydroxypropyl cellulose (that are also thickeners) act to stabilize bFGF. Thus, one of ordinary skill in the art would have been motivated to provide the polysaccharide of Asano et al. in the bFGF composition of Asano et al. for administration with the expectation of administering a stabilized formulation capable of treating periodontal disease. Therefore, the method of claim 9 is obvious over the teachings of Finkenaur and Asano et al.

Regarding claims 12 and 15, Asano et al. teaches that the bFGF composition can treat periodontitis (periodontosis.) Regarding claims 13-14 and 16, Asano et al. teaches that a suitable content of bFGF in the composition can be from 0.001 to 20%, which is the same as the ranges being claimed. Regarding claim 17, Asano et al. teaches that the composition can be administered for repair of periodontal tissue after tooth extraction, and for regeneration of dentin defected by dental caries, as recited in the claim.

Regarding claims 18-19, Asano et al. teaches that the bFGF can be combined with pharmacologically acceptable additives, such as a suspending agent, stabilizer or filling material (see column 4, lines 1-13, in particular), and thus teaches that an inactive and non-toxic additive can be provided. Asano et al. also teaches that the bFGF can be combined with a solvent, and the composition can be prepared by a known method such as dissolution of the bFGF. Finkenaur teaches providing a polysaccharide (thickener) in the composition, as discussed above. Accordingly, the references teach providing the preparation in a solution for dissolution with a thickener and an inactive and non-toxic additive as recited in the claims.

Regarding claims 20-21, Finkenaur teaches the stabilized compositions can be in the form of aqueous medicinal compositions (see page 3, lines 55-60, in particular.)

Regarding the viscosity of the preparation as recited in claims 22-24, it is noted that Finkenaur teaches that the polysaccharide stabilizer can be provided to give a desired viscosity, such as a viscosity in the range of 1-5000 cps (see page 4, lines 55-65, in particular), which overlaps and/or encompasses that claimed. Finkenaur teaches that the increased viscosity improves the residence time of the effective concentration of the growth factor (see page 4, lines 55-64, in particular.) Finkenaur also generally teaches that the amount of cellulose derivative provided can be selected according to the concentration of the growth factor, the type of formulation and the like (see page 3, lines 55-62, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the amount and/or type of the cellulose derivative stabilizing agent provided in the composition, according to the guidance provided by Asano et al. and Finkenaur, to provide a composition having desired stabilization, viscosity and residence time properties. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456,105 USPQ 233,235 (CCPA 1955.)

Regarding claims 25-27, it is noted that as the combined teachings of Asano et al. and Finkenaur renders the claimed composition obvious, the property of such a claimed composition will also be rendered obvious by the prior art teachings, since the properties, namely the stable retention of bFGF over a time period, are inseparable from its composition. Therefore, if the prior art teaches the composition or renders the

composition obvious, then the properties are also taught or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

Response to Arguments

Applicant's arguments and remarks filed October 10, 2007, November 5, 2007 and November 13, 2007 have been fully considered but they are not persuasive.

35 U.S.C. 112, first paragraph

> The Applicant argues that the support for the amended claims is fount in Table I of the specification, which shows activity of 98.9% and 99.1%.

The Examiner disagrees because the amended claims now read on values over 98.9%, in which there is no support.

35 U.S.C. 103(a)

> The Applicant argues that the Declaration has not been fully considered because Ginkenaur teaches the equivalence of hydroxypropyl ether cellulose, methylcellulose, hydroxypropyl cellulose and hydroxypropyl methyl cellulose (see page 3, lines 43-44). The Declaration demonstrates

> a significant difference in stability among these allegedly equivalent materials. Particularly, hydroxypropyl cellulose only showed a 1.3% loss of bFGF, whereas hydroxypropyl methylcellulose showed a loss that was about 4.5X as much and methylcellulose showed a loss that was 6X as much. Further, the limitation that the hydroxypropyl ether derivative of cellulose contains 53.4-77.5% of hydroxypropyl group when a dried material is determined is not taught or suggest by Finkenaur or Asano alone or in combination.

The Examiner disagrees for reasons given in the previous office action. Particularly, Finkenaur teaches the desirability of using water soluble cellulose derivatives to impart the stability enhancement, and furthermore teaches that "the solubility of the cellulose derivatives is determined by the degree of substitution (D.S.) of ether groups and the stabilizing derivatives useful in the present invention should have a sufficient quantity of such ether groups per an hydroglucose unit in the cellulose chain to render the derivatives water soluble" (see page 3, lines 44-48, in particular), and thus Finkenaur teaches that the water-solubility and thus stabilization properties of the polysaccharides can vary according to the degree of substitution of the compounds. Furthermore, it is noted that properties such as the length of the polysaccharide can affect the solubility and thus the stabilization properties of the polysaccharide. Accordingly, the fact that a composition having hydroxypropyl cellulose can be prepared to provide a remaining ratio of bFGF after 7 days of 94.9%, and compositions comprising methyl cellulose or hydroxypropyl methyl cellulose can be prepared that result in a less than 88% remaining ratio of bFGF, is not considered unexpected, as Finkenaur teaches that the solubility, and thus the stabilization properties of the polysaccharide are dependent upon not only the type of polysaccharide used, but also

for example upon the degree of substitution of the polysaccharide. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the desired polysaccharides, and to optimize and/or adjust the degree of substitution of the polysaccharides, as well as other contributing stability factors such as the polysaccharide molecular weight, to provide a composition having the desired stability. Thus, it is considered that Applicants do not provide sufficient evidence of unexpected results in comparison to the closest prior art.

Declaration

> The declaration of Ohkuma demonstrates comparative experiments between hydroxypropyl cellulose (HPC), methyl cellulose (MC) and hydroxypropyl methyl cellulose (HPMC) in regards to stability. HPC showed good stability of the bFGF of 95% after preservation at 25% for 7 days versus 87.6% for MC and 85.5 % for HPMC (see page 4, Table 1). Since the standard content of a medicament is generally determined in the rage of 95 to 105%, MC and HPMC fall below this standard. Additionally, 5% change from the initial content in the drug product stabilization test is defined as "significant change in quality", in which MC and HPMC decreased up to about 10%. Thus, Ohkuma believes that these results would indeed be surprising and could never be expected from the description of the cited references.

The Examiner does not find the results of the declaration persuasive for the reasons given in the previous office action and the previous paragraph above. Particularly, Finkenaur teaches that the solubility, and thus the stabilization properties of the polysaccharide are dependent upon not only the type of polysaccharide used, but also for example upon the degree of substitution of the polysaccharide. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made

would have found it obvious to provide the desired polysaccharides, and to optimize and/or adjust the degree of substitution of the polysaccharides, as well as other contributing stability factors such as the polysaccharide molecular weight, to provide a composition having the desired stability. Thus, it is considered that Applicants do not provide sufficient evidence of unexpected results in comparison to the closest prior art.

Conclusion

No claims allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KENDRA D. CARTER whose telephone number is (571)272-9034. The examiner can normally be reached on 7:30 am - 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/K. D. C./
Examiner, Art Unit 1617

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617